unpredictable with respect to trimerization and folding/binding properties. However, the Examiner only stated a conclusion without providing any factual or scientific data to support the conclusion of unpredictability. Applicants submit that a statement of unpredictability without any scientific support cannot establish non-enablement for the present invention and accordingly, Appplicants respectfully request that the Examiner provide the scientific support underlying this conclusion.

Applicants submit that there are scientific evidences that enable one of ordinary skill in the art to introduce a ligand into the HI loop of the fiber protein without adverse effects on the folding/binding of the fiber protein. The lengths of the H1 loop of the fiber knobs in different adenovirus serotypes are known to vary significantly, indicating that alterations of the original structure of the loop, such as insertions and deletions, would not drastically alter the correct folding of the entire knob domain (instant specification, page 25, lines 3-15). Hence, with the knowledge of the known structure of the fiber knob domain and the known positions of non-conserved amino acids that are not involved in forming proper fiber protein secondary structure, one of ordinary skill in the art would have a reasonable expectation of being able to insert a ligand into the loop regions of the fiber protein without causing significant changes to the folding/binding of the fiber protein.

The Examiner further asserted that "it remains unpredictable if modification introduced into the HI loop domain of the fiber knob can enhance gene transfer into primary tumor cells". However, the Examiner did not show any factual basis upon which the conclusion of unpredictability was based. In contrast, enhanced gene transfer to primary tumor cells was indeed demonstrated in the present application with ovarian cancer cells obtained from patients (page 97, line 12 to page 98, line 8, Figure 17; page 100, line 20 to page 101, line 11, Figure 19), primary tumor explants (Example 29, Figure 20) and primary explant of human SCCHN cells (Example 33, Figure 25). These data illustrate that the modified adenovirus of the present invention can mediate significant enhancement of gene transfer to primary tumor cells through a coxsackievirus and adenovirus receptor-independent pathway. Hence, Applicants respectfully submit that the scope of the claims 1-4 and 6-7 in the instant application has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully submit that the rejection of claims 1-4 and 6-7 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 16, 18-20 and 22 are drawn to a method of increasing the ability of an adenovirus to transduce primary tumor cells by

introducing a ligand into the HI loop domain of the fiber knob of the adenovirus. As discussed above, Applicants submit that there are scientific evidences that enable one of ordinary skill in the art to introduce a ligand into the HI loop of the fiber protein without adverse effects on the folding/binding of the fiber protein. Furthermore, Applicants' specification has demonstrated the modified adenovirus disclosed herein mediated enhanced gene transfer to primary tumor cells such as ovarian cancer cells obtained from patients (page 97, line 12 to page 98, line 8, Figure 17; page 100, line 20 to page 101, line 11, Figure 19), primary tumor explants (Example 29, Figure 20) and primary explant of human SCCHN cells (Example 33, Figure 25) by adenovirus modified with a ligand inserted into the H1 loop. Hence, Applicants respectfully submit that the scope of the claims 16, 18-20 and 22 in the instant application has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 6-7, 16, 18-20 and 22 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 9, 11-15 and 23 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claim 9 is drawn to an adenovirus of the present invention further comprises a herpes simplex virus-thymidine kinase gene. Claims 11 is drawn to a method of using the virus of claim 9 and ganciclovir to kill tumor cells in an individual. The Examiner maintained that any modification introduced into the HI fiber loop region is unpredictable with respect to trimerization and folding/binding properties. However, the Examiner only stated a conclusion without providing any factual or scientific data to support the conclusion of unpredictability. As discussed above, Applicants submit that there are factual and scientific data available to enable one of ordinary skill in the art to introduce a ligand into the HI loop of the fiber protein without adverse effects on the assembly and function of the fiber protein.

The Examiner argued that the art of gene therapy was unpredictable at the time of filing of the instant invention. Applicants submit that the method of killing tumor cells by administering adenovirus that carries herpes simplex virus-thymidine kinase (HSV-tk) gene to an individual followed by ganciclovir treatment is a standard treatment procedure that is currently used in a number of gene therapy trials. Even if the art of gene therapy was unpredictable, the method of killing tumor cells by administering adenovirus that carries HSV-tk gene to an individual followed by ganciclovir treatment is well known in the

art. Claims 9 and 11-12 are not drawn to gene therapy *per se*; the claims are drawn to an improved method of HSV-tk plus ganciclovir treatment using adenovirus of the present invention. Hence, it does not require undue experimentation for one of ordinary skill in the art to practice this method of killing tumor cells using the modified adenovirus of the present invention.

Claim 23 is a dependent claim of claim 16 which is drawn to a method of enhanced gene transfer using the adenovirus of the present invention. As discussed above, claim 16 is fully supported by the data disclosed in the present specification. Hence, Applicants respectfully submit that the scope of the claims 9, 11-12 and 23 in the instant application has a reasonable correlation to the scope of the enablement provided. Claims 13-15 have been canceled. Accordingly, Applicants respectfully request that the rejection of claims 9, 11-15 and 23 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 13-15 were rejected under 35 U.S.C. §112, second paragraph, for omitting essential steps. However, since claims 13-15 have been canceled, the rejection is moot.

The 35 U.S.C. §102 Rejection

Claims 1-4, 6-9, 16, 18-20 and 23 were rejected under 35 U.S.C. §102(e) as being anticipated by **Wickham** et al. The rejection is respectfully traversed.

The biologic basis of infectivity enhancement demonstrated in Applicants' specification is on the basis of CAR-independent gene transfer as a means to circumvent target cell CAR deficiency. Applicants' data demonstrate increased gene transfer to target cells via the HI loop modified adenoviral vectors.

Claims 1-4, 6-9 in the instant invention are drawn to a modified adenovirus that mediates enhanced gene transfer to primary tumor cells. Claims 16, 18-20 and 23 are drawn to a method of using such modified adenovirus to enhance gene transfer to primary tumor cells. As discussed above, the present invention provides data that show the claimed adenovirus mediates enhanced gene transfer to primary tumor cells (Figures 17, 19, 20, 25). Generation of a modified adenovirus that mediates enhanced gene transfer to primary tumor cells and the method of using such modified adenovirus to enhance gene transfer to primary tumor cells were not taught or suggested in **Wickham** et al.

The Examiner argued that **Wickham** et al. is replete with recitations of a modified adenovirus that enhances gene transfer in cells,

including tumor cells. Applicants respectfully disagree. Even though **Wickham** et al. taught modifications of adenovirus, **Wickham** et al. did not teach or suggest an adenovirus with such modifications would mediates enhanced gene transfer to primary tumor cells as claimed herein (column 8, lines 55-66; column 13-14; column 27).

Table 3 in column 36 of **Wickham** et al. disclosed an adenovirus modified by insertion of a ligand into the C-terminal of the fiber knob (Example 10, column 35). In contrast, the present invention claims an adenovirus modified by inserting a ligand into the HI loop of the fiber protein. Moreover, Table 3 showed gene transfer data in kidney cells, smooth muscle cells and endothelial cells, not tumor cells. In contrast, the instant invention presents data and claims a method of using such modified adenovirus to enhance gene transfer to primary tumor cells (Figures 17, 19, 20, 25). Hence, **Wickham** et al. does not teach or suggest each and every aspect of the present invention. The present invention is different and distinct from **Wickham** et al. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 6-9, 16, 18-20 and 23 under 35 U.S.C. §102(e) be withdrawn.

This is intended to be a complete response to the Final Office Action mailed February 28, 2001. Applicants submit that the pending claims are now in condition for allowance. If any issues remain

outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: July 18, 2001

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